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FAX TRANSMITTAL

Date	June 23, 2006
Our File	44893-0004
To	Commissioner of Patents and Trademarks
Company	United States Patent and Trademark Office
Fax number	~~703-308-4556~~ 571-273-8300
From	Charles Boulakia
Number of pages including this one	13
Original	By Mail ___ By Courier ___ Not Sent __x__
Re:	**UNITED STATES – Patent Application Serial No. 10/788,466** **Applicant: Delex Therapeutics Inc.** **Inventor: HUNG, Orlando, Ricardo SHAFER, Steven, Louis PLIURA, Diana, Helen** **Title: OPIOID DELIVERY SYSTEM**

Message

ATTN: James H. Alstrum-Acevedo

Enclosed please find a response to the restriction requirement mailed May 25, 2006 with respect to the above-noted patent application.

PLEASE CONTACT Charles Boulakia AT 416-865-3518
IF YOU HAVE ANY QUESTIONS OR COMMENTS REGARDING THIS TRANSMISSION

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CANADA'S INTELLECTUAL PROPERTY AND TECHNOLOGY LAW FIRM

June 23, 2006 571-273-8300
BY FACSIMILE: 1(~~703-308-4556~~)

United States Patent and Trademark Office
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C.
20231

Attention: James H. Alstrum-Acevedo – Examiner

Dear Sirs:

Re: UNITED STATES: Patent Application No. 10/788,466
Applicant: Delex Therapeutics Inc.
Title: OPIOID DELIVERY SYSTEM
Our File: 44893-0004

This is in response to the restriction requirement mailed May 25, 2006.

ELECTION WITH TRAVERSE

The Examiner has required restriction of the claims of the above-noted application to one of the following inventions, under 35 U.S.C 121:

I. Claims 1 to 36 drawn to an opioid formulation classified in class 424 subclass 43.

II. Claims 37 to 38 drawn to a method of administration of an opioid formulation to provide analgesia classified in class 514, subclass 613.

III. Claims 39 to 43 drawn to a pulmonary drug deliver device classified in class 128.00, subclass 200.14.

IV. Claims 44 to 45 drawn to an opioid administration kit classified in class 206, subclass 570.

V. Claim 46 drawn to the use of an opioid formulation in the manufacture of a medicament classified in class 514, subclass 613.

Claim 47 was not mentioned by the Examiner. It appears that Claim 47 belongs in Group II.

Applicant elects Group I with traverse.

The Examiner has stated that inventions I and II are related as product and

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process of use. The examiner states that the inventions are distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product is claimed can be used in a materially different process of using that product. The Examiner contends that, in the instant case, the product as claimed can be used in a method of treating addiction to heroin by the administration of methadone (an opioid). Applicant respectfully traverses this objection. Claims 37 and 38 specify that the concentration and type of each opioid and amount of and particle size of the formulation delivered from the device on each inhalation is selected so that during inhalation analgesia is achieved before the onset of side effects and onset of side effect occurs before the onset of toxicity. The administration of methadone for treating addiction to heroin does not result in analgesia, because if a dosage of methadone is used which results in analgesia, the treatment for addiction will merely reinforce the addiction. In support, Applicant has enclosed information on methadone treatment, which states that the proper maintenance dose is one at which narcotic craving is averted – without creating euphoria, sedation or analgesia. As such claims 37 and 38 cannot be used in a method of treating addiction to heroin by the administration of methadone.

The Examiner has stated that inventions of Groups II and III are related as process and apparatus for its practice. The Examiner contends that the inventions are distinct if it can be shown that either (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. The Examiner contends that, in this case, the apparatus can be used in a method of treating respiratory diseases. Applicant respectfully traverses this objection. Claims 39 to 43 are indeed drawn to a pulmonary drug delivery device. However, the pulmonary drug delivery device comprises a container containing a formulation comprising an effective amount of at least one rapid onset opioid and a pharmaceutically acceptable carrier (see claim 39). Applicant respectfully submits that a pulmonary drug delivery device comprising a rapid onset opioid could not be used in a method of treating respiratory diseases. Respiratory disease are not treated with opioids, since opioids are respiratory depressants. In support, applicant has enclosed information on opioids and their effects as respiratory depressants.

The Examiner has stated that inventions of Groups IV and I are related as combination and subcombination. Specifically the Examiner contends that inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not record the particulars of the subcombination as claimed for patentability and (2) that the subcombination has utility by itself or in other combinations. The Examiner states that, in the instant case, the subcombination has separate utilities such as a medical formulation administered

parenterally or orally to treat addiction to heroin. As discussed above in traversal to a division of purported inventions of Groups I and II, the subcombination does not have separate utility such as a medical formulation administered parenterally or orally to treat addiction to heroin.

The Examiner contends that the purported inventions of Groups II and IV are related as process and apparatus for its practice. Specifically, the Examiner has stated that the inventions are distinct if it can be shown that either (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. The Examiner contends that, in this case the process can be practiced using a tool as in a syringe to administer an opioid utilized in the treatment of addiction to heroin, or alternatively can be practiced by the oral ingestion of a solid opioid dosage form (e.g. a tablet of methadone) utilized in method of treating heroin addiction. Applicant again respectfully traverses; as stated above, the invention at hand cannot be used for the treatment of methadone or in a method of treating heroin addiction. As set out in claim 39, line 11, of Group III, the drug delivery device is used for analgesic effect. The quantity of methadone required for analgesic effect is addiction-causing, not addiction treating.

The Examiner has objected to inventions of Group III and IV as related as combination and subcombination. Specifically the Examiner has stated that inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability and (2) that the subcombination has utility by itself or in other combinations. The Examiner contends that, in the instant case, the subcombination has separate utilities such as a device for the administration of drugs to treat respiratory diseases, such as salmeterol xinafoate. Applicant respectfully traverses this objection. Salmeterol xinafoate is a beta 2 adrenergic agonist and not an opioid. As such, the subcombination could not be used as a device for the administration of drugs to treat respiratory diseases such as salmeterol xinafoate since, as set out in claim 39, line 3 of Group III, it contains an effective amount of at least one rapid-onset opioid. Group IV also contains an opioid formulation (see claim 44).

The Examiner has objected to Group V as a use claim which contains no identifiable step and is therefore not drawn to patentable subject matter per 35 U.S.C. 101. Applicant respectfully submits that claim 46 is a typical "use for the manufacturer of medicament" claim and is in suitable form for examination.

Favourable re-consideration and allowance of this application are respectfully requested.

This response is being forwarded to you by facsimile transmission to the Patent Examination Office (fax number 703-308-4556), with the original following by courier/ regular mail and trust this will be in order.

Yours very truly,

RIDOUT & MAYBEE LLP

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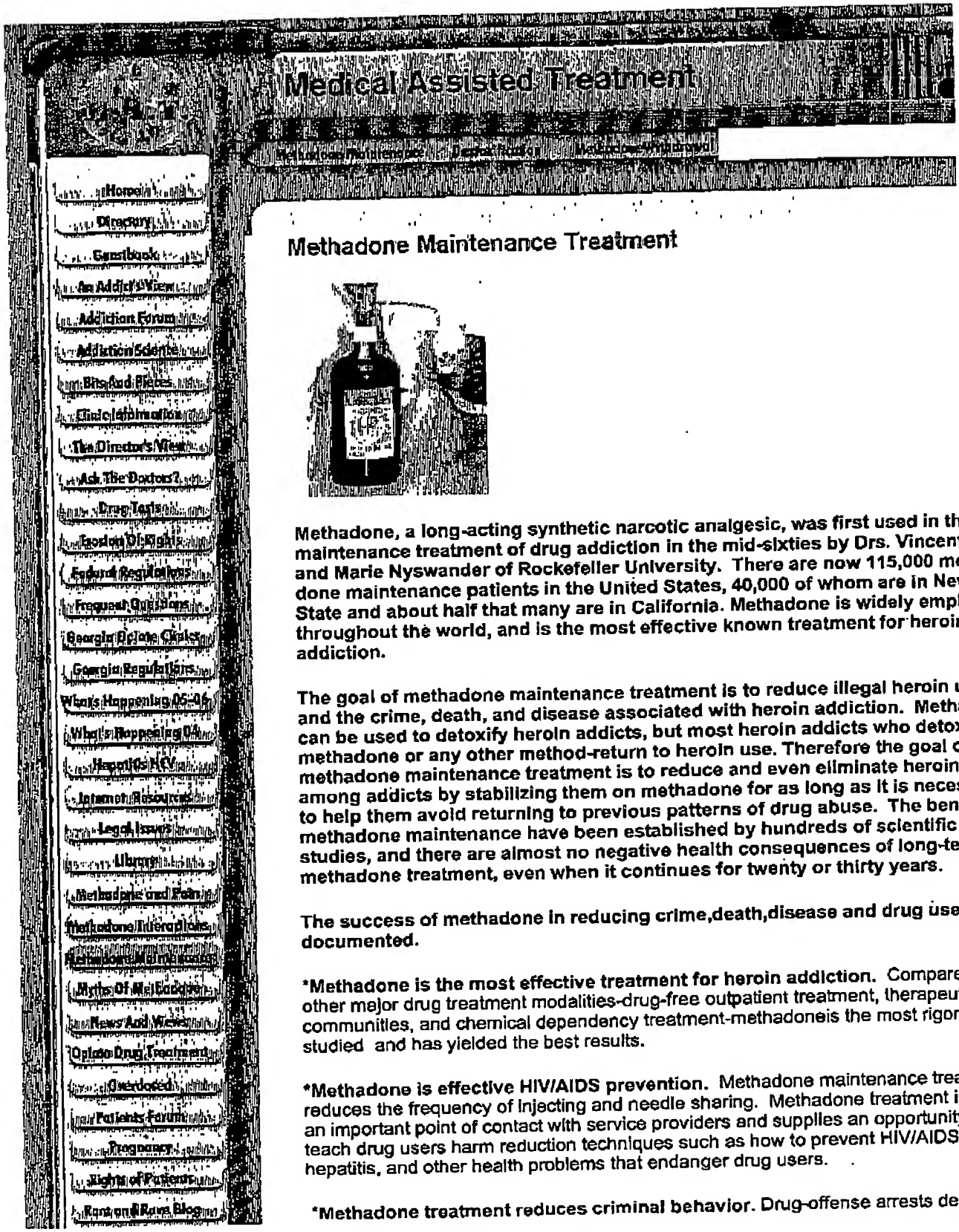
CCB:kak



Methadone Maintenance Treatment

Methadone, a long-acting synthetic narcotic analgesic, was first used in th maintenance treatment of drug addiction in the mid-sixties by Drs. Vincent and Marie Nyswander of Rockefeller University. There are now 115,000 me done maintenance patients in the United States, 40,000 of whom are in Nev State and about half that many are in California. Methadone is widely empl throughout the world, and is the most effective known treatment for heroin addiction.

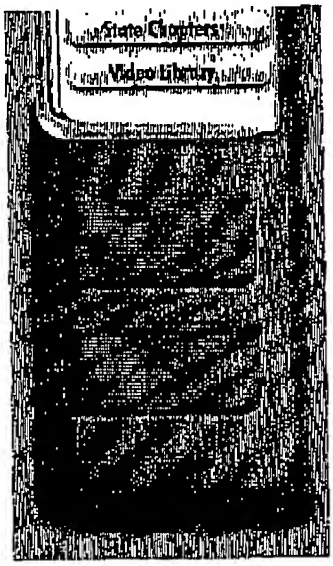
The goal of methadone maintenance treatment is to reduce illegal heroin u and the crime, death, and disease associated with heroin addiction. Metha can be used to detoxify heroin addicts, but most heroin addicts who detox methadone or any other method-return to heroin use. Therefore the goal of methadone maintenance treatment is to reduce and even eliminate heroin among addicts by stabilizing them on methadone for as long as it is neces to help them avoid returning to previous patterns of drug abuse. The bene methadone maintenance have been established by hundreds of scientific studies, and there are almost no negative health consequences of long-ter methadone treatment, even when it continues for twenty or thirty years.

The success of methadone in reducing crime,death,disease and drug use i documented.

***Methadone is the most effective treatment for heroin addiction.** Comparec other major drug treatment modalities-drug-free outpatient treatment, therapeutic communities, and chemical dependency treatment-methadoneis the most rigoro studied and has yielded the best results.

***Methadone is effective HIV/AIDS prevention.** Methadone maintenance treat reduces the frequency of injecting and needle sharing. Methadone treatment is an important point of contact with service providers and supplies an opportunity teach drug users harm reduction techniques such as how to prevent HIV/AIDS, hepatitis, and other health problems that endanger drug users.

***Methadone treatment reduces criminal behavior.** Drug-offense arrests decli



because methadone maintenance treatment patients reduce or stop buying and illegal drugs. Arrests for predatory crimes decline because methadone maintena treatment patients no longer need to finance a costly heroin addiction, and becau treatment allows many patients to stabilize their lives and obtain legitimate employment.

***Methadone drastically reduces, and often eliminates, heroin use among addicts.** The Treatment Outcome Prospective Study (TOPS)-the largest contemporary controlled study of drug treatment-found that patients drastically reduced their heroin use while in treatment, with less than 10% using weekly or after just three months in treatment. After two or more years, heroin among methadone maintenance treatment patients declines, on average to 15% pretrea levels. Often the use of other drugs-including cocaine, sedatives, and alcohol-al declines when an opiate addict enters methadone treatment, even though methe has no direct pharmacological effect on non-opiate use.

***Methadone is cost effective.** Methadone Maintenance Treatment, which cost the average about $4,000 per patient, per year, reduces the criminal behavior associated with illegal drug use, promotes health, and improves social productivi of which serves to reduce the societal costs of drug addiction. Cost benefit anal indicated savings of $4 to $5 dollars in health and social costs for every dollar sp methadone maintenance treatment. Incarceration costs $20,000 to $40,000 per Residential Drug Treatment Programs are significantly more expensive than Methadone Maintenance Treatment, at a cost of $13,000 to $20,000 per year, t it should be noted that treatment stays are typically no more than one year in the programs. Finally given that only only 5 to 10% of the cost of Methadone Mainte Treatment actually pays for the medication itself, methadone could be prescribe delivered even less expensively through physicains in general medical practice, service clinics, and pharmacies.

***Methadone is effective outside of traditional clinic settings.** Methadone in United States is generally restricted to specialized methadone clinics, which are subject to a host of counseling and other service requirements mandated by Fed State, and Municipal Regulators. Though limited, experiments with providing methadone through alternate means have had positive results.

***Limited Service Methadone Maintenance.** Limited Service Methadone Maintenance Treatment Services to addicts who cannot or will not access comprehensive methadone programs. Though limited service programs may not effective as the best full service programs, their patients do substanially reduce and typically fare better than illicit drug users not enrolled in any program.

***Physician Prescribing.** Methadone Maintenance Treatment as part of genera medical practice is increasingly common throughout Europe, Australia, New Zea and Canada, but it is severely restricted in the United States of America. A few "Medical Maintenance Experiments" in the United States, which permitted some methadone recipients to transfer from Traditional Clinics to Office-Based Physicians have achieved excellent treatment results. Medical Maintenance is c effective, and patients often prefer it over Traditional Methadone Clinics.

Questions About Methadone

If you feel you cannot stop using, before y inject again, think of all the liabilities that before you, disease, crime, loss of your husband and children, loss of your job, poverty and possibly death from overdosi Give methadone a try???

How does Methadone work? Methadone is an opiate agonist which has a seri actions similiar to those of morphine and other narcotic medications. Heroin addi are physically dependent on opiate drugs and will experience withdrawal sympto and narcotic cravings if the concentration of opiates falls below a certain level. T **proper dose both wards off acute withdrawal symptoms and markedly redu chronic narcotic cravings by stabilizing blood levels with the drug and its metabolites, thereby permitting "normal functioning".** In Methadone Mainte Treatment, tolerance is deliberately induced to a stable dose of methadone that sufficiently high functioning to block the narcotic and euphoria of methadone an other opiates.

Does methadone make patients "high" and interfere with normal functionir No. Used in maintenance treatment, in proper doses, methadone does not creat euphoria, sedation, or analgesia. Methadone has no adverse effects on motor s mental capacity, or employability.

What is the proper dose of methadone? Doses must be individually determin due to differences in metabolism, body weight, and opiate tolerance. The proper mainte-nance dose is one at which narcotic craving is averted -without creating euphoria, sedation, or analgesia -for 24-36 hours Doses of 60-100mg and some more, are required for most patients; doses below 60mg are almost always insuf for patients who wish to abstain from heroin use.

Is methadone more addictive than heroin? Physical dependence and toleran a drug are part of addiction, but they are not the whole story. Addiction is characterized by compulsive use of a drug despite adverse consequences. The methadone maintenance patient is no more an addict than the terminal cancer p who is physically dependent on morphine, or the diabetic person who is depend insulin. They do not seek out the drug in the absence of withdrawal symptoms a their lives do not revolve around drug use.

Is methadone harder to kick than heroin? Symptoms of abrupt withdrawal an qualitatively similiar when the amount of drug use is pharmacologically equivaler withdrawal from heroin tends to be intense and fairly brief, while the methadone drawal is less acute and longer lasting. Withdrawal symptoms can be ameliorate tapering the dose over an extended period of time.

Is methadone treatment for life? Some patients remain in methadone treatme more than ten years, and even for the rest of their lives, but they constitute a mir (5 to 20%) of patients.

How long should treatment last? Generally the lenght of time spent in treatme postively related to treatment success. The duration of treatment should be individually and clinically determined, and the treatment should last as long as th physician and the individual patient agree is appropriate. Federal and often Stat Regulations require annual evaluation of patients to determine whether they sho continue in Methadone Maintenance Treatment.

Does methadone interfere with good health? Scientific studies have shown t the most significant health consequence of long-term methadone maintenance is marked improvement in general health. Concerns about methadone's effects on immune system and on the kidneys , liver, and heart have been laid out to rest. Methadone's most common side effects-constipation and sweating-usually fade time and are not serious health hazards.

Is it safe to take methadone in pregnancy? Methadone Maintenance Treatme during pregnancy does not impair the child's developemental and cognitive functioning. Indeed it is the medically recommended course of treatment for opia dependent pregnant women.

Is Methadone Maintenance appropriate for all drug users? No. Methadone treatment for opiate dependence, and is not appropriate for individuals who use are not, and have not been, dependent. There are also drug-free treatment options and increasingly, other medications-including buprenorphine, LAAM, anc naltrexone-that be appropriate for some users. Outside the United States, some active drug users are being prescribed heroin, codeine, morphine and injectable morphine.

Is methadone a desirable street drug, with high potential for drug abuse? Though methadone is sometimes sold on the illicit drug market, most buyers of diverted methadone are active heroin users who won't or can't get into a methad program. The extent of of abuse associated with diverted methadone is small rel to heroin, co-caine, and primary addiction to methadone is rare. With improper u methadone, like that of almost any drug, can lead to overdose, overdose deaths attributed to methadone alone are few compared to heroin deaths. In its 1994 statement of emer-gency room incidents, the Drug Abuse Warning Network note fifteen deaths, two-hundred fifty-one morphine/heroin deaths and thirteen aspiri deaths. Finally all methadone deaths are not neccessarily caused by illicitly purchased methadone, some are the results of accidental or inappropriate consumption of legally obtained methadone; often in combination with alcohol or other drugs.

¶ TREATMENT OF OPIATE ADDICTION AS A METABOLIC DISEASE

In the nineteen sixties, researchers at The Rockefeller Universitybegan to questi prevailing theories of addiction that were predicated on prevailing psychological attributes of addicted persons and conditioning theory. Dole and Nyswander (19 indicated in an article addressing these ideas that heroin addiction may be a metabolical disease. Clinical and laboratory studies suggest that the relapse-provoking narcotic hunger is symtomatic of a metabolic dysfunction within the endogenous opiate receptor-ligand system results from repeated use of opiates.

Although some patients function normally without medication after a period of treatment, the majority experience a return of drug hunger. If they do not reenter treatment, they are likely to relapse despite being motivated to remain abstinent and attempt to function normally within the community. Therefore, Methadone Maintenance is a corrective, not a curative procedure of indefinite du (Dole 1970; Kreek 1973, 1976)

Kreek studied subjects who detoxified from heroin or methadone and who succe in remaining abstinent from narcotics. She observed during abstinence there wa persistent abnormal neuroendocrine effects in both goups and has speculated th abnormal responses in neuroendocrine functioning can contribute to relapse (Kr 1986 1988)/ With new analytic techniques available and the discovery of specifi ligands that bind to receptors. Dole supports the renewed interest subject of prol abstinence syndrome.

METHADONE AND DENTAL HEALTH

The following notes from the Concord Hospital Dependency Seminar held in Aus summarize the issues and provide recommendations for dental health.

"Dental problems in addiction treatment subjects. Does methadone rot tee Can we prevent dental decay?

Main speaker: Dr. Peter Foltyn (Dentist, St Vincent's Hospital)

Dr. Halliman began by reminding us how much a smile is worth at a job interview as well as the draw backs of bad breath and poor nutrition which so common in dependency cases. He invited the large audience (of over 4 benefit from Dr. Foltyn's 20 year experience in treating such patients in his practice at Darlinghurst, Syndney.

Dr. Foltyn gave us all a timely reminder of the importance of good dental c and the pitfalls of a number of factors countering dental hygiene. He dealt a number of important issues for patients with drug and alcohol problems including xerostomia (dry mouth). When the salivary mechanism is inhibit there is a breakdown of the normal manner of diluting and removing debris resulting in a lower pH and an acidic environment of the teeth. This allows penetration of the enamel especially at the gingival margins where it is thir and where it joins the dentine.

Thus for patients who are taking antidepressants, anticholinergics and for patients on methadone there is a need to counter dry mouth. The use of 'sı and rinse' at the time of medication (and at other times during the day and can be very effective in protecting the teeth. Chewing gum can stimulate salivation and sugar-free gums are now available.

Regular brushing after each meal, however, is still the mainstay of treatme /prevention. We were told that a medium brush with small, angled head is and that much modern tooth paste is either is either unnecessary and in s cases may cause irritation to already delicate buccal surfaces. This, we w told, was largely due to the foaming agent used in virtually all proprietary b available in supermarkets. Sodium laurel sulfate has been shown to increa irritation is some people but they are currently only two brands available (I at chemist shops) which omit the use of this chemical. The other agents common to most tooth pastes an abrasive agent as well as a detergent. It be that brushing with just water is as effective as and less irritating to som people than using some pastes. We were told that while some electric toot brushes have certain advantages, they are not necessary for optimal denta care.

Another common cause of xerostomia in the hospital setting is head and n radiotherapy. It can be devastating for the teeth that occasionally extractic are recommended before radiation starts since healing is often so protract afterwards. Also, infections can set in, including one type of osteomyelitis which is almost untreatable.

We were shown some shocking Technicolor anatomy-atlas-type-dental sof to demonstrate these matters. Once getting over the initial shock of close dental views we then looked at projections of sequential x-rays of dentitior various states of dissolution (literally). Some were in AIDS cases, others nutritional deficiencies, radiation stomatitis and cancer cases, including Kaposi's sarcoma. Plaque was discussed in length, as well as the various of dealing with it. It was pointed out that in some cases plaque can extend under the gingival margins, requiring tooled removal by the dental surgeor Other exposed areas were dealt with and we were reminded about individu brushing, tooth by tooth on the three surfaces, lingua, buccal, and interfac

Gentle but purposive brushing to engage the gingival margin was stressed Minor bleeding in inflamed areas is to be expected for a time but continuec bleeding should always be examined by the dentist. Flossing to clean the dental surfaces should also be done regularly. Three times yearly check-u patients at increased risk was also stressed.

Topical fluoride should be applied in such high-risk individuals and the dei fluoride 'tray' is the most effective way. It is like a mouth guard which sho be smeared with fluoride paste/gel and inserted for ten minutes before reti Dr. Foltyn said that dentists will apply the same thing for a fee, but to do it oneself regularly is most appropriate for most of our patients. It would app that fluoride can be effective even in late stage dental wear and tear.

We were advised to tell our patients with poor dentition to avoid strong mo washes with alcohol bases such as Listerine. A water-based mouth-wash v antiseptic is more appropriate and less likely to cause irritation. Chemists advise on the types.

The methadone "syrup" marketed in Australia still contains sorbitol which sugar. Although it is not actively absorbed and is safe for diabetics, as a s it is still a fuel for oral bacteria and alcohol with other constituents are not to help dental hygiene. The sugar-free 'solution' Biodone should probably our 'first line' product and the 'syrup' mainly used for those sensitive patie who are unable to tolerate the pure medicine. But importantly, Dr. Foltyn s that this must not give any false sense of dental security as xerostomia wil occur to the same degree with both products...

The use of buprenorphine may also cause dental problems although one w hope to a lesser degree than oral methadone syrup. We need to watch car with this new medication and advise regular dental check-ups.

There are many other issues which had to be left to another session and th was lively discussion on this pressing issue. We need to examine better analgesia during and after dental surgery in dependency patients. Antibio those with heart murmurs, prosthetic joints, etc. need to be addressed. Pu more resources into high risk cases should be a public health priority as g teeth can improve self-confidence, job prospects and even romance.

Modified: July 2, 2005

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Note: Performing your original search, ***respiratory disease opioid***, in PubMed will retrieve *1716* citations.

All: 1 Review: 1

1: Am Rev Respir Dis. 1990 Oct;142(4):895-909. Related Articles, Links

Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression.

Shook JE, Watkins WD, Camporesi EM.

Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710.

In summary, these findings indicate the importance of designing future experiments that delineate between opioid and nonopioid forms of respiratory disease and dysfunction, and the need to identify means of diagnosing them in order to achieve successful recovery. Apparently there is great diversity between animal species in terms of contributions of endogenous opioids to tonic control of ventilation, and future work should strive to identify which species is most appropriate as a model of human ventilatory control and disease. Certain opioid receptor types appear to be linked to independent respiratory functions. For instance, mu receptors in the brain stem produce strong inhibitory actions on respiratory parameters, including RR, VT, VE, and CO2 sensitivity. These effects have been observed in vivo and by electrophysiologic recordings in vitro. Delta receptors may also exert some inhibitory effect on respiration, especially in the NTS. In the CNS, the ventral surfaces of the medulla and pons, especially the NTS and NA, seem to be important sites for opioid-induced inhibition of respiration, whereas the spinal cord probably is not involved in opioid-mediated ventilatory depression. Kappa receptors appear to be devoid of respiratory depressant activity, whereas sigma receptors may stimulate some ventilatory parameters. Morphine and similar pure mu agonists, such as fentanyl and oxymorphine, probably produce their analgesic and respiratory depressant effects through stimulation of mu receptors. Mixed agonists/antagonists that have mu antagonist (or partial agonist) activity plus kappa agonist and/or sigma agonist activity show a ceiling effect for respiratory depression. Future tests need to determine which opioid receptor may be responsible for the ceiling effect. In addition,

the effects of mu, delta, kappa, and sigma selective agonists on hypoxic drive should also be determined, as a drug that stimulates hypoxic sensitivity in the face of hypercapnic depression may produce less overall respiratory depression due to counteractive effects. In the future, clinically optimal opiates should have more specificity of action than those available now. This may be achieved by creating drugs selective for single receptors or by creating drugs with desirable combinations of receptor selectivities. The combinations of mixed agonists/antagonists with pure mu agonists currently in use today are promising, as they provide analgesia with reduced respiratory depression. In the early days of opiate research and development, combination drug regimens were thoroughly tested to determine the "ideal ratios" that would retain analgesic properties but not the other undesirable effects such as respiratory depression (196).(ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:
- Review

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